PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A01N 37/10, C07C 321/16

A1

(11) International Publication Number: WO 99/40787

(43) International Publication Date: 19 August 1999 (19.08.99)

(21) International Application Number: PCT/US99/02678

(22) International Filing Date: 8 February 1999 (08.02.99)

(30) Priority Data:
60/074,694 13 February 1998 (13.02.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/074,694 (CON)
Filed on 13 February 1998 (13.02.98)

(71) Applicant *(for all designated States except US)*: MEDINOX, INC. [US/US]; Suite 201, 11575 Sorrento Valley Road, San Diego, CA 92121 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: LAI, Ching-San [US/US]; 209 Lolita Street, Encinitas, CA 92024 (US).

(74) Agent: REITER, Stephen, E.; Gray Cary Ware & Friedenrich LLP, Suite 1600, 4365 Executive Drive, San Diego, CA 92121 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: MODIFIED PHARMACOLOGICALLY ACTIVE AGENTS AND IMPROVED THERAPEUTIC METHODS EMPLOYING SAME

(57) Abstract

In accordance with the present invention, there are provided modified forms of pharmacologically active agents (e.g., anti-inflammatory agents) which provide increased/prolonged circulating levels of the active agent, thereby allowing administration of reduced levels of the agent to the recipient. This not only reduces the cost of drug, it also reduces the level to which the recipient is exposed to potentially harmful agents. Invention compounds provide a new class of pharmacologically active agents which cause a much lower incidence of side effects due to the benefits obtained by modifying the pharmacologically active agents as described herein.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Modified Pharmacologically Active Agents and Improved Therapeutic Methods Employing Same

FIELD OF THE INVENTION

The present invention relates to novel modified forms of pharmacologically active agents, and methods for the preparation and use thereof. In a particular aspect of the invention, methods are provided for treating a pathological condition with a modified pharmacologically active agent, which requires administration of reduced levels of the pharmacologically active agent, yet provides prolonged circulating levels thereof.

BACKGROUND OF THE INVENTION

Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although non-steroid anti-inflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to the use of NSAIDs (see, for example, J. L. Wallace, in Gastroenterol. 112:1000-1016 (1997); A. H. Soll et al., in Ann Intern Med. 114:307-319 (1991); and J. Bjarnason et al., in Gastroenterol. 104:1832-1847 (1993)).

There are two major ulcerogenic effects of NSAIDs: (1) topical irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to design and develop new NSAIDs that reduce the damage to the

gastrointestinal tract. These efforts, however, have largely been unsuccessful. For example, enteric coating or slow-release formulations designed to reduce the topical irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of clinically significant side effects, including perforation and bleeding (see, for example, D. Y. Graham et al., in Clin. Pharmacol. Ther. 38:65-70 (1985); and J. L. Carson, et al., in Arch. Intern. Med., 147:1054-1059 (1987)).

Since anthracyclines such as adriamycin are commonly used antitumor agents, considerable efforts have also been made to develop strategies for reducing the acute and delayed cardiomyopathies induced by anthracyclines, while maintaining the therapeutic efficacy of these compounds. The molecular mechanism of cardiomyopathy is now attributed to the adriamycin-induced release of iron from intracellular iron proteins, resulting in the formation of an adriamycin-iron complex. The adriamycin-iron complex generates reactive oxygen species, causing the scission and condensation of DNA, peroxidation of phospholipid membranes, depletion of cellular reducing equivalents, interference with mitochondrial respiration, and disruption of cell calcium homeostasis (see, for example, Myers et al., in Science 197:165-167 (1977); and Gianni et al., in Rev. Biochem. Toxicol. 5:1-82 (1983)). In addition to cardiomyopathy, adriamycin administration causes cutaneous irritation and alopecia, mucositis (stomatitis and esophagitis), phlebosclerosis and hematologic toxicities and many other local and systemic toxicities.

Accordingly, there is still a need in the art for modified forms of NSAIDs, and other pharmacologically active agents, which cause a reduced incidence of side-effects, relative to the incidence of side-effects caused

by such pharmacologically active agents as aspirin, ibuprofen, and the like.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided modified forms of pharmacologically active agents (e.g., anti-inflammatory agents) which provide increased/prolonged circulating levels of the active agent, thereby allowing administration of reduced levels of the agent to the recipient. This not only reduces the cost of drug, it also reduces the level to which the recipient is exposed to potentially harmful agents. Invention compounds provide a new class of pharmacologically active agents which cause a much lower incidence of side-effects due to the benefits obtained by modifying the pharmacologically active agents as described herein.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds comprising a pharmacologically active agent containing a readily cleavable thiocarbonyl sulfide substituent thereon. Upon exposure of invention compounds to suitable physiological conditions, carbon disulfide will be released as a result of cleavage of the bond by which the carbonyl sulfide is linked to said pharmacologically active agent (e.g., by hydrolysis).

As employed herein, the phrase "suitable physiological conditions" refers to the physiological conditions at which the desired cleavage occurs. For example, oral administration of a modified pharmacologically active agent according to the invention subjects the linkage by which the carbonyl sulfide is bound to the agent to the acidic conditions of the stomach, which

would likely induce hydrolysis of the compound and release of carbon disulfide therefrom.

Administration of invention compounds allows a protected (i.e., temporarily inactive) form of the active agent to be delivered--becoming active only when the thiocarbonyl sulfide is cleaved therefrom. Administration of invention compounds also allows concurrent delivery of carbon disulfide along with the pharmacologically active agent, thereby reducing the degree to which the active agent is degraded in the body prior to reaching the desired site of action. This, in turn, allows delivery of reduced loads of the active agent to the recipient. Reduced dosage lessens the propensity of high potency drugs to induce undesirable side reactions. In addition, the presence of carbon disulfide allows the active agent to remain in circulation for prolonged periods of time, thereby enhancing the efficacy of the drug.

Diseases and conditions contemplated for treatment in accordance with the present invention include inflammatory and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast, melanoma, carcinoma, and the like), cardiopulmonary bypass, ischemic/reperfusion injury,

gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDA, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.

Pharmacologically active agents contemplated for modification in accordance with the present invention include:

NSAIDs, such as acetaminophen (Tylenol, Datril, etc.), aspirin, ibuprofen (Motrin, Advil, Rufen, others), choline magnesium salicylate (Triasate), choline salicylate (Anthropan), diclofenac (voltaren, cataflam), diflunisal (dolobid), etodolac (lodine), fenoprofen calcium (nalfon), flurobiprofen (ansaid), indomethacin (indocin, indometh, others), ketoprofen (orudis, oruvail), ketorolac tromethamine (toradol), magnesium salicylate (Doan's, magan, mobidin, others), meclofenamate sodium (meclomen), mefenamic acid (relafan), oxaprozin (daypro), piroxicam (feldene), sodium salicylate, sulindac (clinoril), tolmetin (tolectin), meloxicam, nabumetone, naproxen, lornoxicam, nimesulide,

indoprofen, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like;

analgesics/antipyretics (e.g., aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine sulfate, oxycodone hydrochloride, codeine phosphate, dihydrocodeine bitartrate, pentazocine hydrochloride, hydrocodone bitartrate, levorphanol tartrate, diflunisal, trolamine salicylate, nalbuphine hydrochloride, mefenamic acid, butorphanol tartrate, choline salicylate, butalbital, phenyltoloxamine citrate, diphenhydramine citrate, methotrimeprazine, cinnamedrine hydrochloride, meprobamate, and the like);

sedatives/hypnotics (e.g., barbiturates (e.g., pentobarbital, pentobarbital sodium, secobarbital sodium), benzodiazapines (e.g., flurazepam hydrochloride, triazolam, tomazeparm, midazolam hydrochloride, and the like);

antianginal agents (e.g., beta-adrenergic blockers, calcium channel blockers (e.g., nifedipine, diltiazem hydrochloride, and the like), nitrates (e.g., nitroglycerin, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, and the like));

antianxiety agents (e.g., lorazepam, buspirone hydrochloride, prazepam, chlordiazepoxide hydrochloride, oxazepam, clorazepate dipotassium, diazepam, hydroxyzine pamoate, hydroxyzine hydrochloride, alprazolam, droperidol, halazepam, chlormezanone, and the like);

antidepressants (e.g., doxepin hydrochloride, amoxapine, trazodone hydrochloride, amitriptyline hydrochloride, maprotiline hydrochloride,

phenelzine sulfate, desipramine hydrochloride, nortriptyline hydrochloride, tranylcypromine sulfate, fluoxetine hydrochloride, doxepin hydrochloride, imipramine hydrochloride, imipramine pamoate, nortriptyline, amitriptyline hydrochloride, isocarboxazid, desipramine hydrochloride, trimipramine maleate, protriptyline hydrochloride, and the like);

antipsychotic agents (e.g., haloperidol, loxapine succinate, loxapine hydrochloride, thioridazine, thioridazine hydrochloride, thiothixene, fluphenazine hydrochloride, fluphenazine decanoate, fluphenazine enanthate, trifluoperazine hydrochloride, chlorpromazine hydrochloride, perphenazine, lithium citrate, prochlorperazine, and the like);

antimanic agents (e.g., lithium carbonate),

antiarrhythmics (e.g., bretylium tosylate, esmolol hydrochloride, verapamil hydrochloride, amiodarone, encainide hydrochloride, digoxin, digitoxin, mexiletine hydrochloride, disopyramide phosphate, procainamide hydrochloride, quinidine sulfate, quinidine gluconate, quinidine polygalacturonate, flecainide acetate, tocainide hydrochloride, lidocaine hydrochloride, and the like);

antihypertensive drugs, such as diuretics (hydrochlorothiazide, chlorthalidone, metolazone, indapamide, furosemide, bumetanide, torsemide, triamterene, amiloride, spronolactone), beta-adrenergic blocking agents (acebutolol, atenolol, betaxolol, cartelol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol), angiotensin converting enzyme inhibitors (benazepril, captopril, enalapril, fosinopril, quinoapril, ramimpril, losartan), calcium channel-blocking agents

(diltiazem, verapamil, amlodipine, felodipine, isradipine, nicardipine, nifedipine), aplha-adrenoceptor blocking agents, sympatholytics, and vasodilators (such as prazosin, terazosin, doxazosin, clonidine, guanabenz, guanfacine, methylodopa, guanethidine, guanethidine monosulfate, reserpine, hydralazine, minoxidil, and the like), as well as agents such as trimethaphan camsylate, phenoxybenzamine hydrochloride, pargyline hydrochloride, deserpidine, diazoxide, rescinnamine, sodium nitroprusside, rauwolfia serpentina, alseroxylon, phentolamine mesylate, and the like;

antihistamine/antipruritic drugs, such as ethanolamines (e.g., diphenhydramine, diphenhydramine hydrochloride, clemastine, clemastine fumarate, and the like), ethylenediamines (e.g., brompheniramine, brompheniramine maleate, chlorpheniramine, chlorpheniramine maleate, dexchlorpheniramine maleate, triprolidine, triprolidine hydrochloride, and the like), phenothiazines (e.g., promethazine), piperidines (e.g., hydroxzine, hydroxyzine hydrochloride, terfenadine, astemizole, azatadine, azatadine maleate, and the like), cyproheptadine, cyproheptadine hydrochloride, loratidine, carbinoxamine maleate, diphenylpyraline hydrochloride, phenindamine tartrate, tripelennamine hydrochloride, methdilazine hydrochloride, trimprazine tartrate, and the like;

immunosuppressants, such as glucocorticoids (methylprednisolone), myelin basic protein (e.g., 7-capaxone), anti-Fc receptor monoclonal antibodies, hydroorotate dehydrogenase inhibitor, anti-IL2 monoclonal antibodies (e.g., CHI-621 and dacliximab), buspirone, castanospermine, CD-59

(complement factor inhibitor), 5-lipoxygenase inhibitor (e.g., CMI-392), phosphatidic acid synthesis antagonists, ebselen, edelfosine, enlimomab, galaptin, platelet activating factor antagonists, selectin antagonists (e.g., ICAM-4), interleukin-10 agonist, macrocylic lactone, methoxatone, mizoribine, OX-19, peptigen agents, PG-27, protein kinase C inhibitors, phosphodiesterase IV inhibitor, single chain antigen binding proteins, complement factor inhibitor, sialophorin, sirolimus, spirocyclic lactams, 5-hydroxytryptamine antagonist, anti-TCR monoclonal antibodies, CD5 gelonin and TOK-8801, and the like;

antimetabolite cytotoxics (azathioprine, cyclophosphamide), C5a release inhibitor, benzydamine, peldesine, pentostatin, SDZ-ASM-981, thalidomide, benzoporphyrin derivatives, arachidonate antagonists (e.g., halometasone, halobetasol propionate), corticosteriod (clobetasol propionate), growth hormone antagonists (octapeptide somatostatin analogue, lanreotide, angiopeptin and dermopeptin), thymopentin, and the like;

neuroprotective agents, such as α-adrenoreceptor antagonist (i.e, α-dihydroergocryptine), NMDA antagonists (e.g., 5,6,7-tichloro-THQTQ, remacemide, 2-piperazinecarboxylic acid, N-indologlycinamide derivatives, spiro[benzo(b)thiophen-4(5H) derivatives, CP-101606, eliprodil, dexanabinol, GV-150526, L-695902, L-701324, amantadine derivatives, dizocilpine, benzomorphan derivatives, aptiganel, (S)-α-phenyl-2-pyridine ethanamide dihyrochloride and 1-amino-cyclopentanecarboxylic acid), sodium channel antagonists (e.g., 619C89), glycine antagonists (e.g., glystasins), calcium channel antagonists

(e.g., 3,5-pyridinedicarboxylic acid derivatives, conopeptides, 1-piperazineethanol, thieno[2,3-b]pyridine-5-carboxylic acid derivatives, NS-3034, nilvadipine, nisoldipine, tirilazad mesylate, 2H-1-enzopyran-6-ol, nitrone spin traps, iacidipine, iomeerzine hydrochloride, lemildipine, lifarizine, CPC-304, efonidipine, F-0401, piperazine derivatives), calpain inhibitors, fibrinogen antagonists (e.g., ancrod), integrin antagonists (e.g., antegren), thromboxane A_2 antagonist (e.g., 9H-carbazole-9-propanoic acid derivatives, 5-Heptenoic acid derivatives and 1-azulenesulfonic acid derivatives), brain-derived neurotropic factor, adrenergic transmitter uptake inhibitor (e.g., 1-butanamine), endothelin A receptor antagonists (e.g., benzenesulfonamide derivatives, GABA A receptor antagonists (e.g., triazolopyrimidine derivatives and cyclohexaneacetic acid derivatives), GPIIb IIIa receptor antagonists (e.g., C68-22), platelet aggregation antagonist (e.g., 2(1H)-quinolinone derivatives, 1H-pyrrole-1-acetic acid derivatives and coumadin), Factor Xa inhibitor, CPC-211, corticotropin releasing factor agonist, thrombin inhibitor (e.g., cothrombins, fraxiparine, dermatan sulfate and heparinoid), dotarizine, intracellular calcium chelators (e.g., BAPTA derivatives), radical formation antagonists (EPC-K1, 3-pyridinecarboxamide derivatives, superoxide dismutase, raxofelast, lubeluzole, 3H-pyrazol-3-one derivatives, kynurenic acid derivatives, homopiperazine derivatives, and polynitroxyl albumin), protein kinase inhibitors (e.g., 1H-1,4-diazepine), nerve growth agonist (e.g., floor plate factor-5), glutamate

antagonist (e.g., cyclohexanepropanoic acid, riluzole, NS-409 and acetamide derivatives), lipid peroxidase inhibitor (e.g., 2,5-cyclohexadiene-1,4-dione derivatives), sigma receptor agonist (e.g., cyclopropanemethanamine derivatives and SA-4503), thyrotropin releasing hormone agonist (e.g., JTP-2942, L-prolinamide and posatirelin), prolyl endopeptidase inhibitor, monosialoganglioside GM1, proteolytic enzyme inhibitor (e.g., nafamostat), neutrophil inhibitory factor, platelet activating factor antagonist (e.g., nupafant), monoamine oxidase B inhibitor (e.g., parafluoroselegiline and benzonitrile derivatives), PARS inhibitors, Angiotensin I converting enzyme inhibitor (e.g., perindopril and ramipril), acetylcholine agonist (e.g., pramiracetam), protein systhesis antagonist (e.g., procysteine), phosphodiesterase inhibitor (e.g., propentofylline), opioid kappa receptor agonist (e.g., 10H-phenothiazine-2-carboxamine derivatives), complement factor inhibitor (sCRI fragments), somatomedin-1, carnitine acetyltransferase stimulant (e.g., acetylcarnitine), and the like;

T cell inhibitors such as synthetic leucocyte antigen derived peptides, interleukin-1 receptor antagonist, MG/AnergiX, anti-CD3 monoclonal antibodies, anti-CD23 monoclonal antibodies, anti-CD28 antibodies, anti-CD2 monoclonal antibodies, CD4 antagonists, anti-E selectin antibodies, MHC inhibitors, monogens, mycophenolate mofetil, LRA-1 inhibitors, selectin inhibitors, and the like;

antimigraine agents, such as MK-462, 324C91, Phytomedicine, (S)-fluoxetine, calcium channel antagonists (e.g., nimodipine/Nimotop, flunarizine, dotarizine/FI-6026, iomerizine HCL/KB-2796,

CPC-304, and CPC-317), α-dihydroergocryptine, 5-HT1 agonists, (e.g., Sumatriptan/Imitrex, Imigran, GR-85548, 311C, and GR-127607), 5-HT1D agonists, 5-HT1A antagonists, 5-HT1B antagonists (e.g., CP-93129), 5-HT1D antagonists (e.g., 1H-indole-5-ethanesulfonamide derivatvies and 1H-indole-5-methanesulfonamide), 5-HT1D receptor cloned (e.g., 5-HT1D agents), 2-thiophenecarboxamide, 3-piperidinamine, diclofenac potassium, dihydroergotamine (e.g., DHE 45®), ergotamine tartrate, dolasetron mesilate, dotarizine, flupirtine, histamine-H3 receptor agonist, indobufen, 1-azulenesulfonic acid derivatives, cholinesterase inhibitors, (e.g., S-9977), bradykinin antagonists, nitric oxide reductase inhibitors (e.g., BN-52296), nitric oxide receptor antagonists, substance P antagonists (e.g., Capsaicin/Nasocap), endopeptidase inhibitors (e.g., neutral endopeptidase, cloned), piperazine derivatives, neurokinin 1 antagonists, metergoline, dopamine D2 antagonist (e.g., metoclopramide + lysine acetyl), enkephalinase inhibitors (e.g., neutral endopeptidase), 5-HT2 antagonists (e.g., LY-053857), 5-HT3 antagonists (e.g., Dolasetron mesilate/MDL-73147, and 4H-carbazol-4-one derivatives), tenosal, tolfenamic acid, cyclooxygenase inhibitors (e.g., carbasalate/carbaspirin calcium, and tenosal/MR-Y134), alpha adrenoreceptor antagonists (e.g., arotinolol, and dihydroergocryptine), opioid agonists (e.g., flupirtine/D-9998), beta adrenergic antagonists (e.g., propranolol), valproate semisodium, propanolol hydrochloride, isometheptene mucate, dichloralphenazone, and the like;

antiarthritic agents, such as anti-CD4 monoclonal antibodies, phospholipase A1 inhibitor, loteprednol, tobramycin, combinations of loteprednol and tobramycin, salnacedin, amiprilose, anakinra, anergiX, anti-B7 antibody, anti-CD3H, anti-gp39, anti-MHC MAbs, antirheumatic peptides, anti-Tac(Fv)-PE40, AP-1 inhibitors, AR-324, purine nucleotide phosphorylase inhibitors (e.g., BCX-5), bindarit, CD2 antagonist (e.g., BTI-322), campath-1H, CD4 antagonist (e.g., CE9.1 and SB-210396), tumor necrosis factor antagonist (e.g., p80 TNFR, rhTNFbp, peptide T, CenTNF, thalidomide, CDP-571 and TBP-1), cobra venom factor, interleukin 1a agonist (e.g., cytogenin), interleukin 2 receptor antagonist (e.g., dacliximab), ICAM 1 antagonist (e.g., enlimomab), interleukin 1 beta converting enzyme inhibitors (e.g., ICE-inhibitors), interferons (e.g., thymocartin), interleukin-10, interleukin-13, interleukin 1 antagonist (e.g., SR-31747 and TJ-114), interleukin-2 antagonist (e.g., sirolimus), phospholipase C inhibitor, neurokinin 1 antagonist (e.g., L-733060), laflunimus, leflunomide, leucotriene antagonists, levamisole, LFA3TIP, macrocyclic lactone, MHC class II inhibitors, mizoribine, mycophenolate mofetil, NfkB inhibitors, oncolysin CD6, peldesine, pidotimod, PKC-RACK inhibitors, PNP inhibitors, reumacon, CD28 antagonist, roquinimex, RWJ-50271, subreum, T7 vector, tacrolimus, VLA antagonist (e.g., TBC-772), transforming growth factor beta agonist, methionine synthase inhibitors (e.g., vitamin B12 antagonist), adenosine A2 receptor agonist (e.g., YT-146), CD5 antagonist (e.g., zolimomab), 5-lipoxygenase inhibitor (e.g., zileuton, tenidap, and ABT-761), cyclooxygenase inhibitor

(e.g., tenoxicam, talmetacin, piroxicam, piroxicam cinnamate, oxaprozin, NXTHIO, ML-3000, mofezolac, nabumetone, flurbiprofen, aceclofenac, diclofenac, and dexibuprofen), metalloproteinase inhibitor (e.g., XR-168, TNF convertase inhibitors, GI-155704A, AG-3340 and BB-2983), nitric oxide synthase inhbitors (i.e, ARL-16556), phospholipase A2 inhibitor (e.g., ARL-67974), selectin antagonist (e.g., CAM inhibitors), leucotriene B4 antagonist (e.g., CGS-25019C), collagenase inhibitor (e.g., GR-129574A), cyclooxygenase 2 inhibitor (e.g., meloxicam), thromboxane synthase inhibitor (e.g., curcumin), cysteine protease inhibitor (e.g., GR-373), metalloproteinase inhibitor (D-5410), lipocortins synthesis agonist (e.g., rimexolone, predonisolone 21-farnesylate, HYC-141, and deflazacort), chelating agent (diacerein), elastase inhibitors, DNA directed RNA polymerase inhibitor (e.g., estrogens), oxygen radical formation antagonist (e.g., glucosamine sulfate), thrombin inhibitors (e.g., GS-522), collagen inhibitors (e.g., halofuguinone), hyaluronic acid agonist (e.g., NRD-101, hylan, Dispasan, and Hyalart), nitric oxide antagonists (e.g., hydroxocobalamin), stromelysin inhibitors (e.g., L-758354), prostaglandin E1 agonist (e.g., misoprostol, and misoprostol+diclofenac), dihydrofolate reductase inhibitor (e.g., trimetrexate, and MX-68), opioid antagonist (e.g., nalmefene), corticotropin releasing factor antagonist (e.g., NBI-103, and NBI-104), proteolytic enzyme inhibitor (e.g., protease nexin-1, and NCY-2010), bradykinin antagonist (e.g., tachykinin antagonists, and NPC-17731), growth hormone antagonist (e.g., octreotide), phosphodiesterase IV inhibitor (e.g., PDEIV

inhibitors), gelatinase inhibitor (e.g., REGA-3G12), free radical scavengers (e.g., SIDR-1026), prostaglandin synthase inhibitors (e.g., sulfasalazine), phenylbutazone, penicillamine, salsalate, azathioprine, indomethacin, meclofenamate sodium, gold sodium thiomalate, ketoprofen, auranofin, aurothioglucose, tolmetin sodium, and the like;

antigout agents (e.g., colchicine, allopurinol, and the like);

anticoagulants (e.g., heparin, heparin sodium, warfarin sodium, and the like);

thrombolytic agents (e.g., urokinase, streptokinase, altoplase, and the like);

antifibrinolytic agents (e.g., aminocaproic acid);

hemorheologic agents (e.g., pentoxifylline);

antiplatelet agents (e.g., aspirin, empirin, ascriptin, and the like);

anticonvulsants (e.g., valproic acid, divalproate sodium, phenytoin, phenytoin sodium, clonazepam, primidone, phenobarbitol, phenobarbitol sodium, carbamazepine, amobarbital sodium, methsuximide, metharbital, mephobarbital, mephenytoin, phensuximide, paramethadione, ethotoin, phenacemide, secobarbitol sodium, clorazepate dipotassium, trimethadione, and the like);

agents useful for calcium regulation (e.g., calcitonin, parathyroid hormone, and the like);

antibacterial agents (e.g., amikacin sulfate, aztreonam, chloramphenicol, chloramphenicol palmitate, chloramphenicol sodium succinate, ciprofloxacin hydrochloride, clindamycin hydrochloride, clindamycin palmitate, clindamycin phosphate, metronidazole, metronidazole hydrochloride, gentamicin sulfate, lincomycin hydrochloride, tobramycin sulfate, vancomycin hydrochloride,

polymyxin B sulfate, colistimethate sodium, colistin sulfate, and the like);

antifungal agents (e.g., griseofulvin, keloconazole, and the like);

antiviral agents (e.g., interferon gamma, zidovudine, amantadine hydrochloride, ribavirin, acyclovir, and the like);

antimicrobials (e.g., cephalosporins (e.g., cefazolin sodium, cephradine, cefaclor, cephapirin sodium, ceftizoxime sodium, cefoperazone sodium, cefotetan disodium, cefutoxime azotil, cefotaxime sodium, cefadroxil monohydrate, ceftazidime, cephalexin, cephalothin sodium, cephalexin hydrochloride monohydrate, cefamandole nafate, cefoxitin sodium, cefonicid sodium, ceforanide, ceftriaxone sodium, ceftazidime, cefadroxil, cephradine, cefuroxime sodium, and the like), penicillins (e.g., ampicillin, amoxicillin, penicillin G benzathine, cyclacillin, ampicillin sodium, penicillin G potassium, penicillin V potassium, piperacillin sodium, oxacillin sodium, bacampicillin hydrochloride, cloxacillin sodium, ticarcillin disodium, azlocillin sodium, carbenicillin indanyl sodium, penicillin G potassium, penicillin G procaine, methicillin sodium, nafcillin sodium, and the like), erythromycins (e.g., erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, doxycycline hyclate, minocycline hydrochloride, and the like), and the like);

antioxidants (e.g., N-acetylcsysteine, Vitamin A, Vitamin C, Vitamin E, ß-carotene, EUK-8, flavonoids, glutathione, α-lipoic acid, melatonin, retinols, and the like);

anti-infectives (e.g., miconazole, vidarabine, inosine pranobex, vidarabine, inosine prabonex, cefpimizole sodium), fradiomycin, and the like); bronchodialators (e.g., sympathomimetics (e.g., epinephrine hydrochloride, metaproterenol sulfate, terbutaline sulfate, isoetharine, isoetharine mesylate, isoetharine hydrochloride, albuterol sulfate, albuterol, bitolterol, mesylate isoproterenol hydrochloride, terbutaline sulfate, epinephrine bitartrate, metaproterenol sulfate, epinephrine, epinephrine bitartrate), anticholinergic agents (e.g., ipratropium bromide), xanthines (e.g., aminophylline, dyphylline, metaproterenol sulfate, aminophylline), mast cell stabilizers (e.g., cromolyn sodium), inhalant corticosteroids (e.g., flurisolidebeclomethasone dipropionate, beclomethasone dipropionate monohydrate), salbutamol, beclomethasone dipropionate (BDP), ipratropium bromide, budesonide, ketotifen, salmeterol, xinafoate, terbutaline sulfate, triamcinolone, theophylline, nedocromil sodium, metaproterenol sulfate, albuterol, flunisolide, and the like); hormones (e.g., androgens (e.g., danazol, testosterone cypionate, fluoxymesterone, ethyltostosterone, testosterone enanihate, methyltestosterone, fluoxymesterone, testosterone cypionate), estrogens (e.g., estradiol, estropipate, conjugated estrogens), progestins (e.g., methoxyprogesterone acetate, norethindrone acetate), corticosteroids (e.g., triamcinolone, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate, prednisone, methylprednisolone acetate suspension, triamcinolone acetonide, methylprednisolone,

prednisolone sodium phosphate methylprednisolone sodium succinate, hydrocortisone sodium succinate, methylprednisolone sodium succinate, triamcinolone hexacatonide, hydrocortisone, hydrocortisone cypionate, prednisolone, fluorocortisone acetate, paramethasone acetate, prednisolone tebulate, prednisolone acetate, prednisolone sodium phosphate, hydrocortisone sodium succinate, and the like), thyroid hormones (e.g., levothyroxine sodium) and the like), and the like;

hypoglycemic agents (e.g., human insulin, purified beef insulin, purified pork insulin, glyburide, chlorpropamide, glipizide, tolbutamide, tolazamide, and the like);

hypolipidemic agents (e.g., clofibrate, dextrothyroxine sodium, probucol, lovastatin, niacin, and the like);

proteins (e.g., DNase, alginase, superoxide dismutase, lipase, and the like);

nucleic acids (e.g., sense or anti-sense nucleic acids encoding any therapeutically active protein, including the proteins described herein, and the like);

agents useful for erythropoiesis stimulation (e.g., erythropoietin);

antiulcer/antireflux agents (e.g., famotidine, cimetidine, ranitidine hydrochloride, and the like);

antinauseants/antiemetics (e.g., meclizine hydrochloride, nabilone, prochlorperazine, dimenhydrinate, promethazine hydrochloride, thiethylperazine, scopolamine, and the like);

septic shock agents, such as angiogenesis inhibitors (OLX-514), bradykinin antagonists (e.g., CP-0502, and NPC-17731), complement factor inhibitors (e.g., C3 convertase inhibitor), C5a release inhibitors (e.g., CAB-2.1), dopamine agonists

(e.g., dopexamine), elastase inhibitors (e.g., ONO-5046), E selectin antagonists (e.g., CY-1787), farnesyltransferase inhibitors (RBE limonene), immunostimulants (e.g., CGP-19835A, lipid A vaccine, edobacomab, nebacumab, StaphGAM, and diabodies), immunosuppressants (e.g., CytoTAB, and transcyclopentanyl purine analogues), interleukin 1 antagonists (e.g., interleukin 1 receptors), interleukin 1 receptor antagonists (e.g., anakinra), interleukin 1b antagonists (e.g., interleukin-1ß), interleukin 1beta converting enzyme inhibitors (e.g., ICE-inhibitors), interleukin 8 antagonists (e.g., IL-8 receptor), interleukin 13 agonists (e.g., intereleukin-13), ITF-1697, lipase clearing factor inhibitors (e.g., SC-59735), membrane permeability enhancers (e.g., Bactericidal Permeability Increasing protein/BPI), nitric oxide antagonists (e.g., hydroxocobalamin), nitric oxide synthase inhibitors (e.g., L-NMMA, and α-methyl-N-delta-iminoethyl-ornithine), P2 receptor stimulants (e.g., ATP analogues), phosphatidic acid synthesis antagonists (e.g., lisofylline), phospholipase A2 inhibitors (e.g., S-448, acylpyrrole-alkanoic acid derivatives, and indoleacetic acid derivatives), platelet activating factor antagonists (e.g., ABT-299, TCV-309, SM-12502, (2RS,4R)-3-(2-(3-pyridinyl)-thiazolidin-4-oyl)indoles, UR-12670, and E-5880), prostacyclin agonists (e.g., taprostene), prostaglandin E1 agonists (e.g., TLC C-53), protein kinase inhibitors (e.g., SB-203580), protein kinase C inhibitors, protein synthesis antagonists (e.g., procysteine), proteolytic enzyme inhibitors (e.g., nafamostat), SDZ-PMX-622, selectin antagonists (e.g., sulfated glycolipid cell adhesion inhibitors), thrombin

inhibitors (e.g., GS-522), TNF receptor-Ig, tumor necrosis factor antagonists (e.g., anti-TNF MAbs, MAK-195F, TBP-I, Yeda, rhTNFbp, and CDP-571), tumor necrosis factor alpha antagonists (e.g., E-5531), and the like;

multiple sclerosis agents, such as 4-aminopyridine, 15±deoxyspergualin, ACTH, amantadine, antibody adjuvants (e.g., poly-ICLC, and poly-IC+poly-L-lysine+carboxymethylcellulose), anti-cytokine MAb (CDP-835), anti-inflammatory (e.g., CY-1787, and CY-1503), anti-selectin MAb (e.g., CY-1787), anti-TCR MAb (e.g., NBI-114, NBI-115, and NBI-116), bacloten, bethanechol chloride, carbamazepine, carbohydrate drugs (e.g., CY-1503), clonazepam, CNS and immune system function modulators (e.g., NBI-106, and NBI-107), cyclophosphamide, cyclosporine A, cytokines (e.g., IFN-α, alfaferone, IFN-ß 1b, betaseron, TGF-ß2, PEG-TGF-ß2, betakine, IFN-ß/Rebif, frone, interferon-ß, and IFN-ß), CD4+T cell inhibitors (e.g., AnergiX), CD28 antagonists (e.g., B7-1, B7-2, and CD28), directcytotoxicity therapies (e.g., benzoporphyrin derivative (BPD)), FK-506, growth factors (e.g., glial growth factor, GGF, nerve growth factors, TGF-ß2, PEG-TGF-ß2, and betakine), humanized MAb (e.g., anti-IFN-γMAb, smart anti-IFN-γMAb, anti-Tac antibody, and smart anti-Tac antibody), humanized anti-CD4 MAb (e.g., anti-CD4 MAb, centara), hydrolase stimulants (e.g., castanospermine), IFN-α, IFN-γ antagonist (e.g., anti-IFN-γ MAb, and smart anti-IFN-γ MAb), IL-2 antagonists (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, IL-2 fusion toxin, and DAB_{389}IL-2), IL-4 antagonists (e.g., IL-4 fusion toxin, and DAB_{389}IL-4), immune-mediated neuronal damage inhibitors (e.g., NBI-114, NBI-115, and NBI-116),

immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24, and poly-IC+poly-L-lysine+carboxymethyl-cellulose), immunosuppressants (e.g., azathioprine, AI-100 animal protein, rDNA human protein AI-101, peptide, AI-102, castanospermine, tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, anti-leukointegrin MAb, Hu23F2G, primatized anti-CD4 antibody, CE9.1, Galaptin 14-1, GL14-1, Lectin-1, recombinant IML-1, linomide, roquinimex, LS-2616, transcyclo-pentanyl purine analogs, MS-6044, spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCL, NSC-356894, NKT-01, TCR, CD3/Ti, cyclosporine, OL-27-400, SandImmune, Human IL-10, monogens, anti-TCR MAbs, TCAR MAbs, Monogen TM19, Monogen TM27, Monogen TM29, Monogen TM31, peptigen TP12, anti-CD4 MAb, cantara, immunophilins, VX-10367, VX-10393, VX-10428, synthetic basic copolymer of amino acids, copolymer-1, COP-1, T lymphocyte immunofusion (TIF) protein, and cyclophosphamide), integrin antagonists (e.g., anti-integrin (cell adhesion molecule α4ß1 integrin) MAbs, AN-100225, and AN-100226), interferon agonists (e.g., poly-ICLC, and poly-IC+poly-L-lysine+carboxymethyl-cellulose), interferon-ß-1b, isoprinosine, IV methylprednisolone, macrolides (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, and Prograf), MAO B inhibitors (e.g., selegiline, and Parkinyl), methotrexate, mitoxantrone, muscle relaxants (e.g., RGH-5002), muscarinic antagonists (e.g., RGH-5002), neurosteroids (e.g., NBI-106, and NBI-107), octapeptides (e.g., peptide T), oxybutinin chloride, oxygen free radical antagonists (e.g., tetrandrine, biobenzylisoquinoline alkaloid), peptide agonists

(e.g., peptide T), phenoxybenzamine, phospholipase C inhibitors (e.g., edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24), photodynamic therapies (e.g., benzoporphyrin derivative (BPD)), plasmapheresis, platelet activating factor antagonists (e.g., ginkgolide B, and BN-52021), potassium channel antagonists (e.g., aminodiaquine, and EL-970), propranolol, prostaglandin synthase inhibitors (e.g., sulfasalazine, salazosulfa-pyridine, PJ-306, SI-88, azulfidine, salazopyrin), protease antagonists (e.g., ginkgolide B, and BN-52021), recombinant soluble IL-1 receptors, spergualin analogs (e.g., spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCl, NSC-356894, NKT-01), TCR peptide decoys (e.g., NBI-114, NBI-115, and NBI-116), TCR peptidomimetic decoys (e.g., NBI-114, NBI-115, and NBI-116), TCR peptide vaccines (e.g., AI-208 (Vß6.2/6.5 phenotype)), selectin antagonists (e.g., lectin-1, and recombinant IML-1), soluble TNF receptor I, TCARs (e.g., TCR, CD3/Ti, and peptigen TP12), TNF antagonists (e.g., thalidomide, and TNF inhibitors), tricyclic antidepressants, and the like;

organ transplantation agents, such as anti-CD25 MAbs, anti-Tac antibodies, anti-TNF MAb (e.g., CDP571), apoptosin, azathioprines (e.g., imuran), BCX-34, CA3, CD28, complement inhibiting factors (e.g., CD59), CTLA4Ig, cyclosporines (e.g., CsA), FK-506/rapamycin binding proteins (FKBP), glucocorticoids, humanized version of OKT3 (e.g., huOKT3-185), mycophenolate mofetil, hydroorotate dehydrogenase inhibitors (e.g., Brequinar), orthoclone OKT3 (e.g., IgG2a anti-T cell murine monoclonal antibody, and muromonab-CD3), rapamycins (e.g., AY-22989), and streptomyces

isolates (e.g., FR-900520, and FR-900523), and the like;

systemic lupus erythematosus (SLE) agents, such as androgen-derived steriods (e.g., Org-4094), anti-CD4 humanized antibodies, anti-DNA/V-88, anti-idiotypic murine MAb (e.g., anti-idiotypic antibody to 3E10/MAb1C7), CD2 antagonists (e.g., CD2), complement inhibitors (e.g., recombinant MCP-based complement inhibitors), cyclosporines (e.g., Sandimmune, cyclosporine analog, OG-37325, cyclosporin-G, and NVal-CyA), cytokines (e.g., IL-4 fusion toxin), cytokine receptor antagonists (e.g., immunomodulatory cytokines), E-selectin antagonists (e.g., anti-ELAM, and CY-1787), FK506/tacrolimus (e.g., Prograf), hypercalcemic agents (e.g., KH-1060), IFN-γ antagonists (e.g., anti-IFN-γ MAb, and smart anti-IFN-γ MAb), IL-1ß converting enzyme inhibitors (ICE), IL-2 produced by E. coli (e.g., celmoleukin, IL-2, TGP-3, and Celeuk), immunoglobulins (e.g., anti-ELAM, CY-1788, and humanized CY-1787), immunostimulants (e.g., thymotrinan, RGH-0205, and TP3), immunosuppressants (e.g., Rapamycin, AY-22989, NSC-226080, NSC-606698, anti-CD4, T-cell inhibitor, anti-tac MAb, smart anti-tac MAb, Migis (membrane immunoglobulin-isotope specific) antibodies, SM-8849, immunophilins, VX-10367, VX-10393, VX-10428, mycophenolate mofetil, ME-MPA, RS-61444, cyclosporine, OL-27-400, Sandimmune, IL-4 fusion toxin, trypanosomal inhibitory factor (TIF), T-cell receptor, CD3/Ti, Org-4094, anti-TBM, CP 17193, Leflunomide/A-77-1726, ELAM-1, AnergiX, Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, NKT-01, Roquinimex, LS-2616, linomide, LJP-394, and CD-59 antigen), immunotoxins (e.g., Zolimomab aritox,

xmmly-h65-rta, xomazyme-lym/CD5-Plus, OrthoZyme-CD5+, XomaZyme-H65-rta, Xomazyme-CD5 Plus), intravenous immunoglobulins (e.g., IVIG), integrin antagonists (e.g., integrin blockers), Migis™ antibodies, monoclonal antibody therapeutics, murine MAb (e.g., anti-SLE vaccine, and MAb 3E10), primatized anti-CD4 antibodies (e.g., CE9.1), protease inhibitors (e.g., matrix metalloprotease (MMP) inhibitors, and stromelysin), protein synthesis antagonists (e.g., anti-CD6-bR, anti-T12-bR, and oncolysin CD6), purine nucleoside phosphorylase inhibitors (e.g., BCX-25, and BCX-14), selectin antagonists (e.g., CY1503, and Cylexin), spergualin analogues (e.g., Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, and NKT-01), T cell inhibitors (e.g., AnergiX), tumor necrosis factor _ (TNF) antagonists, and the like;

Alzheimer's disease agents, such as ACh release enhancers (e.g., T-588 (benzothiophene derivative)), acetylcholine release stimulants (e.g., DUP-996 and analogues), AMPA agonists (e.g., AMAlex, and Isoxazole compound series), AMPA GluR agonist (e.g., IDRA-21 [7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazinine]), AMPA GluR antagonists (e.g., S-18986, and related quinolone derivatives), anticholinesterases (e.g., E-2020), Ca-antagonists (e.g., NS-649, spider venom-derived ICM peptides and analogues, and substituted 2-aminoindanes compound series), combined anticholinesterase and muscarinic AChR antagonists (e.g., PD142676), K-channel blockers (e.g., Trans-R-4-(4-methoxyphenyl-methyl) cyclohexylanine and analogues, and margatoxin-based functional and/or structural analogues), MI muscarinic receptor agonists

(e.g., Xanomeline), NMDA antagonists (e.g., certain indole derivatives, and (R-(R^1,S^1))-α-(4-hydroxyphenyl)-beta-methyl-4-(phenylmenthyl)-1-piperidinepropanol and analogues), nicotinic AChR agonists (e.g., ABT-418 [isoxazole, 3-meth-5-(1-meth-2-pyrrolidinyl)]), and the like; antiparkinson agents (e.g., ethosuximide, and the like); psoriasis agents, such as 5-LO inhibitors (e.g., Wy-50295, Wy-49232, Lonapalene, RS-43179, MK-886, L-663536, ETH-615, DUP-654, Zileuton, epocarbazolin-A, and A-64077), 5-LO/CO inhibitors (e.g., BF-397, Tenidap, CP-309, and CP-66248), angiogenesis inhibitors (e.g., platelet factor 4), anticancer antibiotic (e.g., AGM-1470, and TNP-470), anti-inflammatory cytochrome P450 oxidoreductase inhibitors (e.g., DuP-630, and DuP-983), antiproliferative compounds (e.g., Zyn-Linker), arachidonic acid analogues (e.g., CD581, and CD554), arachidonic acid antagonists (e.g., Lonopalene, RS-43179, triamcinolone acetonide with penetration enhancer Azone, betamethasone dipropionate steroid wipe, G-202, Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, and Sicorten), beta-glucan receptor antagonists, betamethasone steroid wipes, calcium metabolic moderators (e.g., Tacalcitol, Bonealfa, TV-02 ointment, Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, and Divonex), CD4 binding inhibitors (e.g., PIC 060), cell adhesion compounds (e.g., CY-726, VCAM-1, ELAM-1, and ICAM), cell adhesion inhibitors (e.g., selectin inhibitor, GM-1930), cellular aging inhibitors (e.g., Factor X), corticosteroids (e.g., Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, and Sicorten), cyclosporin analogues (e.g., IMM-125), dihydrofolate reductase inhibitors (e.g., G-301, dichlorobenzoprim,

methotrexate, and methotrexate in microsponge delivery system), E-selectin inhibitors (e.g., ISIS 4730), endogenous active form of vitamin D_3 (e.g., Calcitriol, and Du- 026325), fibroblast growth factor antagonists (e.g., Saporin mitotoxin, and Steno-Stat), fumagillin analogues (e.g., AGM-1470, and TNP-470), G-proteins and signal transduction compounds (e.g., CPC-A), gel formulations for acne (e.g., nicotinamide, N-547, and Papulex), growth hormone antagonists (e.g., Octreotide, Sandostatin, Lanreotide, angiopeptin, BIM-23014, and Somatuline), humanized antibodies (e.g., anti-CD4 antibody), hydroorotate dehydrogenase inhibitors (e.g., Brequinar sodium, bipenquinate, and DuP-785), ICAM-1 inhibitors (e.g., ISIS 939), IL-1 and other cytokine inhibitors (e.g., Septanil), IL-1 converting ezyme inhibitors, IL-1 receptor antagonists (e.g., Antril), IL-2 antagonists (e.g., Tacrolimus, Prograf, and FK-506), IL-2 receptor-targeted fusion toxins (DAB389IL-2), IL-8 receptors, immunostimulants (e.g., Thymopentin, and Timunox), immunosuppressants (e.g., XomaZyme-CD5 Plus, cyclosporine, Sandimmune, SR-31747, anti-CD11, 18 MAb, Tacrolimus, Prograf, FK-506, and FK-507), immunosuppressive agents targeting FK506 (e.g., immunophilins, VX-10367, and VX-10428), immunotoxins MAb directed against CD antigen (e.g., XomaZyme-CD5 Plus), leukotriene antagonists (e.g., Sch-40120, Wy-50295, and Wy-49232), leukotriene B4 antagonists (e.g., SC-41930, SC-50605, SC-48928, ONO-4057, LB-457, LY-255283, LY-177455, LY-223982, LY-223980, and LY- 255253), leukotriene synthesis inhibitors (MK-886, and L-663536), lipase clearing factor inhibitors (e.g., 1-docosanol, and lidakol),

lipid encapsulated reducing agent (e.g., Dithranol), liposomal gel (e.g., Dithranol), LO inhibitors (e.g., CD581, CD554, Masoprocol, and Actinex), lithium succinate ointments (e.g., lithium salts, and Efalith), LO/CO inhibitors (e.g., P-8892, P-8977, CHX-108, and FPL-62064), membrane integrity agonists (e.g., lithium salts, and Efalith), microtubule inhibitors (e.g., Posophyliotoxin-containing compound, and Psorex), octapeptide somatostatin analogues (e.g., Lanreotide, angiopeptin, BIM-23014, and Somatuline), oligonucleotides (e.g., ISIS 4730, ISIS 3801, ISIS 1939, and IL-1 inhibitors), peptide agonists (e.g., octapeptide, and peptide T), PKC inhibitors, phospholipase A2 compounds, pospholipase D compounds, photodynamic anticancer agents (e.g., 5-aminolevulinic acid, and 5-ALA), photodynamic therapies (e.g., benzoporphyrin derivative, synthetic chlorins, synthetic porphyrins, and EF-9), photosensitizer (e.g., Porfirmer sodium), PKC inhibitors (e.g., Safingol, and Kynac), platelet activating factor antagonists (e.g., TCV-309), platelet aggregation inhibitors (e.g., CPC-A), prodrug NSAIDs (e.g., G-201), prostaglandin agonist (e.g., eicosapentaenoic acid + gamma-linolenic acid combination, and Efamol Marine), protein inhibitors (e.g., SPC-103600, and SPC-101210), protein kinase C (PKC) inhibitors (e.g., Ro-31-7549, Ro-31-8161, and Ro-31-8220), protein synthesis antagonists (e.g., Calcitriol, Du-026325, LG-1069, LG-1064, AGN-190168, Namirotene, and CBS-211A), purine nucleoside phosphorylase inhibitors (e.g., BCX-34), radical formation agonists (e.g., benzoporphyrin derivative), recombinant antileukoproteinases (e.g., ALP-242), retinoids (e.g., BMY-30123,

LG-1069, and LG-1064), retinoid derivatives (e.g., AGN-190168), rapamycin binding proteins (FKBP) (e.g., immunophilins, VX-10367, and VX-10428), second generation monoaromatic retinoids (e.g., Acitretin, and Neotigason), soluble IL-1, IL-4 and IL-7 receptors, somatostatin and somatostatin analogues (e.g., Octreotide, and Sandostatin), steroids, (e.g., AGN-191743), streptomyces anulatus isolates (e.g., epocarbazolin-A), superoxide dismutase (e.g., EC-SOD-B), thymidylate synthase inhibitors (e.g., AG-85, MPI-5002, 5-FU in biodegradable gel-like matrix, 5-FU and epinephrine in biodegradable gel-like matrix, and AccuSite), topical formulations (e.g., P-0751, and P-0802), transglutaminase inhibitors, tyrphostin EGF receptor kinase blockers (e.g., AG-18, and AG-555), VCAM-1 inhibitors (e.g., ISIS 3801), vitamin D analogues (e.g., Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, and Divonex), vitamin D_3 analogues (e.g., Tacalcitol, Bonealfa, TV-02 ointment), and vitamin D_3 derivatives (e.g., 1,2-diOH-vitamin D_3), and the like;

diabetes agents, such as ACE inhibitors (e.g., captopril), amylin, amylin agonists and antagonists (e.g., Normylin™, AC137, GC747, AC253, and AC625), autoimmune compounds (e.g., AI-401), capsaicins (e.g., Zostrix-HP), cell regulators (e.g., protein kinase C inhibitors, and Balanol), domperidones (e.g., Motilium®), fluvastatins (e.g., Lescol), FOX 988, fusion toxins (e.g., DAB_{389}IL-2, and DAB_{486}IL-2), gene therapies (e.g., Transkaryotic Therapies), glucagons (e.g., recombinant yeast glucagon), IL-10 compounds, iloprost, immunosuppressives (e.g., tacrolimus, Prograf, and FK-506), proinsulin, insulin and

insulin analogs (e.g., AI-401, Nu-Insulin compounds, Humulin, Iletin, Humalog™, LYs-Pro, and Amaryl), insulin-like growth factors (e.g., Chiron/Ciba-Geigy compounds, Fujisawa compounds, and Genetech compounds), insulinotropins (e.g., Pfizer/Scios Nova compounds), nerve growth factors (e.g., Genentech compounds), oral hypoglycemics (e.g., AS-6, glimepiride, Amaryl, CL 316,243, acarbose, miglitol, recombinant yeast glucagon, GlucaGen™, NovoNorm™, glipizide, insulinotropin, and CI-991/CS-045), platelet-derived growth factors (e.g., Zymo Genetics/Novo Nordisk compounds), sulfonylureas (e.g., tolbutamide, acetohexamide, tolazamide, and chlorpropramide), T cell approaches (e.g., anergize, AnergiX™, Procept compounds, and T cell Sciences compounds), and tolrestats (e.g., Alredase®, and ARI-509), activin, somatostatin, and the like;

stroke agents, such as 5-HT antagonists (e.g., Piperazine derivative), 5-HT reuptake inhibitors (e.g., Milnacipran, and Dalcipran), 5-HT 1A agonists (e.g., SR-57746A, and SR-57746), 5-HT 3 agonists (e.g., SR-57227), 5-HT 4 antagonists, 5-lipoxygenase inhibitors (e.g., low MW dual 5-lipoxygenase and PAF inhibitor CMI-392), ACh agonists (e.g., Pramiracetam, Choline-L-alfoscerate, L-alpha-glycerylphosphoryl-choline, and Delecit), adenosine agonists (e.g., GP-1-4683, ARA-100, and arasine analogs), adenosine A1 receptor agonists (e.g., Azaisotere, 2-chloro-N-[4 (phenylthio)-1-piperidinyl] adenosine, and 2120136), adenosine reuptake inhibitors (e.g., Diphenyloxazole derivatives), adrenergic transmitter re-uptake inhibitors (e.g., Bifemelane, E-0687, MCI-2016, Alnert, and Celeport), aldose reductase inhibitors (e.g.,

Spiro-3' pyrroline derivatives), alpha antagonists (e.g., Drotaverine acephyllinate, and Depogen), alpha 2 agonists (e.g., SNAP-5083, SNAP-5608, and SNAP-5682), AMPA receptor agonists (e.g., heterocyclic compound SYM-1207, and heterocyclic compound SYM-1252), AMPA receptor antagonists (e.g., LY-293558, and LY-215490), Ancrod/Arvin, aspirin, benzothiazoles (e.g., Lubeluzole, and R87926), benzodiazepine receptor antagonists (e.g., 3-oxadiazolyl-1,6-naphthyridine derivatives, Tetracyclic imidazodiazepineseries imidazenil, FID-02-023, and Ro-23-1412), blood substitutes, bradykinin antagonists (e.g., CP-0127, Bradycor, and Septicor), C5a release inhibitors (e.g., protein derivative CMI-46000), calcium antagonists (e.g., Lemildipine, NB-818, NPK-1886, Trimetazidine derivative, Iomerizine KP-2796, Diltiazem analog clentiazem maleate, and TA-3090), calcium channel antagonists (e.g., nitrendipine-like compound diperdipine, YS-201, U-92032, Diltiazem derivative, 1058, SM-6586, KP-840, F-0401, D-31-D, Tetrahydronaphthalene derivatives, fasudil, AT-877, H-7, HA-1044, HA-1077, Eril, darodipine, dazodipine, PY-108-068, Plimo, Dihydropy-ridine, AE 0047, GJ-0956, Lacidipine, GR-43659, GR-43659X, GX-1048, S-312-d, S-312, S-830312, Nilvadipine, and FK-235), calpain inhibitors (e.g., AK-275, and CX-275), carnitine palmitoyl-transferase inhibitors, carvedilol, cerebral calcium antagonist vasodilators (e.g., Nimodipine, and Nimotop), cholinesterase inhibitors (e.g., indole and indazole derivatives, and Tacrine analog), complement factor inhibitors (e.g., TK9C, protein derivative TP16, compinact A, compinact C, Factor D inhibitors, and soluble, recombinant MCP-based

complement inhibitors), complement inhibitors (e.g., sCRI/BRL-55730, and YM-203), coronary vasodilators (e.g., Nicorandil, RP-46417, SG-75, and Adancor), CPC-111, cytidyl diphosphocholine/citicholines, cytokines (e.g., NBI-117), Dexanabiol, dopamine agonists, EAA receptors, endothelin antagonists (e.g., SB 209670), endothelin receptor antagonists, excitatory amino acid agonists (e.g., acylated polyamine analogs, and N-(4-hydroxyphenylpropanonyl)-spermine analog), excitatory amino acid antagonists (e.g., Tryptophan, 4,6-disubstituted stroke & kynurenine derivatives, NPC-17742, CPC-701, and CPC-702), glutamate antagonists (e.g., Kainate quisqualate NNC-07-9202, NPC-17742, small molecule CNS-1237, NS-257, NS-072, BW-619C, CGS 19755, Riluzole, PK-26124, and RP 54274), glutamate receptor antagonists (e.g., Araxin compounds, Quinoxaline derivative, YM-90K, and YM-900), glycine antagonists, glycine NMDA agonists (e.g., 3-hydroxy-2,5-dioxo-1H-benz[b]azepines), glycine NMDA associated antagonists (e.g., 5,6-dihydro-1H-pyrrolo [1,2,3-de] quinoxaline-2,3-diones, Strychnine-insensitive glycine binding site of NMDA receptor L-687414, Glystasins, ACEA-2011, ACEA-3031, AC-1021, ACPC, and eliprodil), growth factor antagonists (e.g., non-peptide indolocarbazole neutrophic molecules, and CEP-075), GPIIb/IIIa antagonists (e.g., Peptide C68-22), hemorheological agents (e.g., Drotaverine acephyllinate, and Depogen), heparin, hydroxyl radical formation inhibitors (e.g., homopiperazine derivative K-7259), hypocalcemic agents (e.g., calcitonin peptide, related to hCGRP peptide), hypothermic agents/BMY-20862, ICAM-1 compounds (e.g., Enlimomab),

immunosuppressants (e.g., small molecule compounds, and NBI-117), integrin general antagonists (e.g., monoclonal antibody AN-100225, and monoclonal antibody AN-100226), Interleukin-1 antagonists (e.g., cyclic nitrones), iron-dependent lipid peroxidation inhibitors (e.g., 2-(amino-methyl) chromans), lactic acid accumulation/inhibitors (e.g., small molecule CPC-211), Leukotriene B4 antagonists (e.g., Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, and RP 61605), lipid peroxidase inhibitors (e.g., Idebenone, and Avan), low molecular weight small molecules, methyltransferase stimulants (e.g., 4-methyl benzenesulfonate, ademetionine sulfate tosilate, FO-156, and Ceritan), monoamine oxidase B inhibitors (e.g., MD-280040, MD-200243, MD-280080, Lazabemide, and Ro-19-6327), MS-153, MS-424, /Na^+/H^+ Na^+/Li^+ exchange inhibitors (e.g., Pyrazine derivatives), nadroparin (e.g., Fraxiparin), nafronyl/naftidrofuryl (e.g., Praxilene), nerve growth factor agonists (e.g., small molecule compounds, CNTF, BDNF, 2.5S NGF, monosialoganglioside GM1, and Sigen/Sygen), neuronal calcium channel blockers (e.g., CPC-304, and CPC-317), neuronal differentiation compounds (e.g., F-spondin), neuropeptide agonists (e.g., Neurotrophic Peptide Trofexin), neutrophil inhibitory factors (e.g., small molecule compounds), nitric oxide agonists (e.g., hydroxy derivative N-3393, hydroxy derivative N-3398, nicorandil, and Therapicon), nitric oxide antagonists, NMDA antagonists (e.g., Spiroisoindoles/dizocilpine derivatives, Oxindole compound, CP-112116, LY-104658, LY-235959, FR-115427, Sialic acid derivative, N-palmitoyl-Betaethylglycoside neuraminic acid, ND-37, Ro-01-6794, 706, Dextrorphan, Ifenprodil

analogue eliprodil, SL-82.0715, Lipophilic molecules, HU-211, Remacemide, 934-423, 12495, 12859, 12942AA, Selfotel, CGS-19755, SDZ-EAA-494, CGP-40116, CGP-37849, CGP-39551, and CGP-43487), NMDA antagonist-partial agonists (e.g., Conantokin G peptide SYM-1010), NMDA channel blockers (e.g., Aptiganel, CERESTAT, and CNS 1102), NMDA receptor antagonists, NMDA receptor subtypes (e.g., Kainate quisqua-late NNC-07-9202), non-competitive NMDA antagonists (e.g., FPL-15896), non-ionic copolymer RheothRx, nootropic/acetylcholine agonists (e.g., Oxiracetam, CT-848, and Neuractiv), norepinephrine inhibitors (e.g., Midalci-pran), N-type calcium channel antagonists (e.g., NS-626, and NS-638), opioid antagonists (e.g., Nalmefene, nalmetrene, JF-1, ORF-11676, Cervene, and Incystene), opioid kappa receptor agonists (e.g., acrylacetamide enadoline, and CI-997), organoselenims (e.g., Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, and RP 61605), oxygen scavengers (e.g., Tirilazad mesylate, Lazaroids, and Freedox), PA2 inhibitors (e.g., phospholipase A2 inhibitor), PAF antagonists (e.g., nupafant, and BB-2113), partial glycine NMDA agonists (e.g., ACPC), peptide/ GPIIb/IIIa antagonists (e.g., Integrelin), peptidic neuron-specific calcium channel antagonists (e.g., SNX-111), phosphodiesterase inhibitors (e.g., Xanthine derivatives, propentofylline, Hoe-285, and Hextol), phospholipase A2 inhibitors (e.g., small organic molecule CEP-217), plasminogen activators (e.g., r-ProUK (recombinant pro-urokinase), platelet-activating factor antagonists (e.g., UK-74505), platelet adhesion inhibitors (e.g., Peptide), platelet aggregation antagonists (e.g., cilostazol, peptide agents, GPHb-IIIA inhibitor,

and TP-9201), platelet aggregation inhibitors (e.g., Diaminoalkanioic acid derivatives), potassium channel agonists (e.g., Nicorandil, RP-46417, SG-75, and Adancor), prolyl endopeptidase (PEP) inhibitors (e.g., JTP-4819), protein kinase C inhibitors (e.g., monosialoganglioside derivative Liga-20), proteolytic enzyme inhibitors (e.g., Protease nexin-1, Incyte, PN-1, PN-2, Nafamostat, FUT-175, Duthan, and Futhan), pyrimidine derivatives, Quinolizine derivatives (e.g., KF-17329, and KF-19863), radical formation antagonists (e.g., EPC-K1), recombinant tissue plasminogen activators (e.g., alteplase, and Activase), Schwann cell derived molecules/promoters, sigma antagonists (e.g., Sigma ligand), sigma receptor antagonists (e.g., tetrahyropyridinyl-isoxazolines and isoxazoles PD-144418), sodium/calcium channel modulators (e.g., Lifarizine, and RS-87476), sodium channel antagonists, streptokinase (e.g., Streptase), substituted guanadine (e.g., small molecule CNS-1237), superoxide dismutase stimulants (e.g., PEG conjugated enzyme superoxide dismutase/Dismutec, and PEG-SOD), thrombin inhibitors, (e.g., non-peptide), thromboxane synthase inhibitors (e.g., Linotroban, and HN-11500), thyrotropin-releasing hormone agonists (e.g., TRH agonists, Protirelin analogthymoliberin, and RX-77368,), ticlopidine (e.g., Ticlid), TJ-8007, TRH agonists (e.g., Thyrotropin releasing hormones, and JTP-2942), trilazard, urokinase (e.g., Abbokinase), w-conopeptide (e.g., SNX-111), and warfarin (e.g., Coumadin), and the like;

agents useful for the treatment of carcinomas (e.g., adriamycin, taxol, interleukin-1, interleukin-2

(especially useful for treatment of renal carcinoma), and the like, as well as leuprolide acetate, LHRH analogs (such as nafarelin acetate), and the like, which are especially useful for the treatment of prostatic carcinoma),

agents useful for the treatment of endometriosis (e.g., LHRH analogs),

agents useful for the treatment of uterine contraction (e.g., oxytocin),

agents useful for the treatment of diuresis (e.g., vasopressin),

agents useful for the treatment of cystic fibrosis (e.g., Dnase (i.e., deoxyribonuclease), SLPI, and the like),

agents useful for the treatment of neutropenia (e.g., GCSF),

agents useful for the treatment of lung cancer (e.g., beta 1-interferon),

agents useful for the treatment of respiratory disorders (e.g., superoxide dismutase),

agents useful for the treatment of ischemia/reperfusion injury (e.g., selectin inhibitors, Irf1, and the like);

nitric oxide synthase inhibitors (e.g., N^4-methyl-L-arginine, aminoguanidine, N^C-(iminoethyl)-L-ornithine, thiocitrulline and other citrulline derivatives, N^4-nitro-L-arginine, N^4-nitro-L-arginine methyl ester, N^4-amino-L-arginine, and other arginine derivatives, isothiourea and its derivatives, and the like,

as well as a variety of other agents, such as acyclovir, alendronate sodium, amlodipine, ampicillin, azelaic acid, azithromycin, beclomethasone, betamethasone, bicalutamide, buspirone, carisoprodol, carvedilol, cefaclor, cefadroxil, cefixime, cefprozil, ceftibuten, cefuroxime axetil, cephalexin, cetirizine hydrochloride, cimetidine,

ciprofloxacin, cisapride, clarithromycin, clavulanate, clonazepam, clotrimazole, codeine, conjugated estrogens, cyclobenzaprine, desogestrel, dexrazoxane, diazepam, dicyclomine HCI, digoxin, diltiazem, dirithromycin, doxazosin, doxycycline, enalapril, erythromycin, erythromycin base, erythromycin stearate, estradiol, ethinyl estradiol, ethynodiol diacetate, etodolac, famotidine, fluconazole, fluoxetine, fluvastatin, furosemide, gemfibrozil, glipizide, glyburide, guaifenesin, hydrochlorothiazide, hydrocodone, hydrocortisone, ibuprofen, ibutilide fumarate, indapamide, insulin, ipratropium bromide, ketoconazole, ketoprofen, ketorolac tromethamine, lamivudine, lansoprazole, levonorgestrel, levothyroxine, lisinopril, loracarbef, loratidine, lorazepam, losartan potassium, lovastatin, medroxyprogestrone, methylphenidate, methylprednisolone, metoprolol, metoprolol tartrate, moexipril hydrochloride, mometasone furoate, mupirocin, mycophenolate mofetil, nabumetone, nalmefene hydrochloride, naproxen, neomycin, nifedipine, nisoldipine, nitrofurantoin, nizatidine, norethindrone, norgestrel, nortriptyline, ofloxacin, omeprazole, oxaprozin, oxycodone, paroxetine, penicillin, pentoxifylline, phenylpropanolamine, phenytoin, polymyxin, porfimer sodium, potassium chloride, pravastatin, prednisone, promethazine, propoxyphene, pseudoephedrine, quinapril, ramipril, ranitidine, riluzole, salmeterol, saquinavir mesylate, sertraline, sevoflurane, simvastatin, sucralfate, sulfamethoxasole, sumatriptan, temazepam, terazosin, terconazole, terfenadine, tetracycline, theophylline, timolol, tramadol, tramadol hydrochloride, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, valproic acid, venlafaxine, verapamil, wafarin, zolpidem, and the like.

The thiocarbonyl sulfide component and the pharmacalogically active agent of invention compounds can be covalently attached employing a variety of linkages,

e.g., disulfide linkages, thioamide linkages, thioether linkages, thioimide linkages, S-glycosidic linkages, and the like. Such linkages can be accomplished using standard synthetic techniques as are well known by those of skill in the art, either by direct reaction of the starting materials, or by incorporating a suitable functional group on the starting material, followed by coupling of the reactants.

In accordance with another embodiment of the present invention, there are provided methods for the preparation of protected forms of pharmacologically active agents, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions. The resulting modified agent provides a latent form of the pharmacologically active agent, releasing the biological activity thereof only when the covalent bond linking the thiocarbonyl sulfide to said pharmacologically active agent is cleaved (e.g., by an esterase, amidase or other suitable enzyme). Cleavage of the covalent bond linking the thiocarbonyl sulfide to said pharmacologically active agent also releases free carbon disulfide, which imparts a drug sparing effect (i.e., reduces the amount of drug required to achieve a therapeutic effect). Release of free carbon disulfide also provides a protective effect on the liver by reducing the amount of active agent which is cleared by the liver.

In accordance with yet another embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of pharmacologically active agent(s) to a subject, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent(s) prior to administration to said subject, wherein said covalent

attachment is susceptible to cleavage under selected physiological conditions.

In accordance with still another embodiment of the present invention, there are provided methods for enhancing the effectiveness of pharmacologically active agent(s), said method comprising covalently attaching a thiocarbonyl sulfide to said pharmacologically active agent, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

In accordance with a still further embodiment of the present invention, there are provided improved methods for the administration of pharmacologically active agent(s) to a subject for the treatment of a pathological condition, the improvement comprising covalently attaching a thiocarbonyl sulfide to said pharmacologically active agent prior to administration of said pharmacologically active agent to said subject, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions, thereby releasing a therapeutically effective amount of carbon disulfide.

In accordance with yet another embodiment of the present invention, there are provided methods for reducing liver injury caused by administration of pharmacologically active agent(s) to a subject, said methods comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent prior to administration to said subject, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

In accordance with still another embodiment of the present invention, there are provided methods for enhancing circulating levels of pharmacologically active agent(s) upon administration to a subject, said methods

comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent prior to administration thereof to said subject, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

In accordance with a still further embodiment of the present invention, there are provided methods to prolong the presence in the circulatory system of a subject of a pharmacologically active agent administered to said subject, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

Those of skill in the art recognize that the modified pharmacologically active agents described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like.

Depending on the mode of delivery employed, the modified pharmacologically active agents contemplated for use herein can be delivered in a variety of pharmaceutically acceptable forms. For example, the active agent can be delivered in the form of a solid, solution, emulsion, dispersion, micelle, liposome, and the like.

Thus, in accordance with still another embodiment of the present invention, there are provided physiologically active composition(s) comprising modified pharmacologically active agents as described herein in a suitable vehicle rendering said compound(s) amenable to oral delivery, transdermal delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound(s) is(are) included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and

palatable preparations. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are

conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Compounds contemplated for use in the practice of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

In general, the dosage of nitric oxide scavenger-containing conjugate of the invention employed as described herein falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr. Typical daily doses, in general, lie within the range of from about 1 μg up to about 50 mg per kg body weight, and, preferably within the range of from 10 μg to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 μg to about 100 mg per kg body weight, and, preferably, within the range of from 10 μg to 10 mg per kg body weight.

In accordance with yet another embodiment of the present invention, there are provided improved methods for the treatment of a subject suffering from a pathological condition by administration thereto of pharmacologically active agent(s), the improvement comprising covalently attaching a thiocarbonyl sulfide to said pharmacologically active agent prior to administration thereof to said subject, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions, thereby releasing a therapeutically effective amount of carbon disulfide.

Thus, invention method for the treatment of a subject afflicted with a pathological condition comprises administering to a subject an effective amount of a modified pharmacologically active agent,

wherein said pharmacologically active agent is effective for treatment of said condition, and

wherein said pharmacologically active agent has been modified by the covalent attachment thereto of a thiocarbonyl sulfide.

The invention will now be described in greater detail by reference to the following non-limiting examples.

Example 1

Evaluation of the effects of thiocarbonyl sulfide-modified ibuprofen on acute gastric mucosal injury

Wistar rats (200-250 grams, male) are fasted overnight but allowed free access to water. Ten rats in each group are given ibuprofen alone or ibuprofen modified according to the invention orally at doses of 10, 20 or 50 mg/kg. The rats are sacrificed five hours later and visible gastric damage is assessed by examining under microscope and histological evaluation.

Example 2

Evaluation of the effects of thiocarbonyl sulfide-modified ibuprofen on chronic gastric ulcer

White New Zealand rabbits (male, about 1 kg) are given subcutaneously ibuprofen alone or ibuprofen modified according to the invention at a dose of 30 mg/kg for every 12 hours. The animals are sacrificed on day 4 (after the 7th dose) and the visible ulcers in the stomach are examined and measured with calipers. The tissue samples are fixed in neutral buffered formalin and processed for histological evaluation.

Example 3

Evaluation on the anti-inflammatory effects of dithiocarbonyl sulfide-modified ibuprofen

Wistar rats (male, 200-250 g) are fasted overnight but allowed to free access to drinking water. Ibuprofen alone or ibuprofen modified according to the invention is given orally at a dose of 1, 10, or 30 mg/kg (6 animals each group). After one hour, the rats are anesthetized and 0.1 ml of lambda carrageenan (0.1% solution) is injected into the right hind foot pad. The volume of the pad is measured by hydroplethysmometry every hour for the next five hours.

Example 4

Evaluation of the effects of dithiocarbonyl sulfide-modified ibuprofen on prostaglandin synthesis

Wistar rats (male, 200-250 g) are fasted overnight but allowed free access to drinking water. The rats are anesthetized and their backs are shaved. After an incision to the back, a sponge (2.5 x 1 x 0.5 cm) soaked with 2 ml of 0.5% carrageenan is implanted. Five hours later, the rats (6 animals in each group) are given orally

either ibuprofen alone or ibuprofen modified according to the invention at a dose of 30 mg/kg or vehicle control. One hour later, the rat is sacrificed and the sponge is carefully removed. The exudate is recovered from the sponge and the prostaglandin E2 level in the exudate is measured by enzyme-linked immunosorbent assay.

Example 5

Evaluation on the protective effects of thiocarbonyl sulfide-modification against adriamycin-induced cardiotoxicity

Balb/c mice (male, 20-25 g) are fed a standard diet and allowed free access to drinking water. The mice are anesthetized and the telemetry system consisting of implantable transmitters, a telemetry receiver and analog ECG adapter is implanted in the peritoneal cavity of each mouse. After surgery, the mice are allowed to recover for two weeks. The mice are given intravenously either adriamycin alone or adriamycin modified according to the invention at a dose of 4 mg/kg through the tail vein. The treated mice are observed for two weeks. The body weight, ECG and heart rate are recorded daily. At the end of the study, the animals are sacrificed and the hearts are processed for histological evaluation.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A compound comprising a pharmacologically active agent containing a cleavable thiocarbonyl sulfide substituent thereon.

2. A compound according to claim 1 wherein said pharmacologically active agent is selected from NSAIDs, analgesics/antipyretics, sedatives/hypnotics, antianginal agents, antianxiety agents, antidepressants, antipsychotic agents, antimanic agents, antiarrhythmics, antihypertensive drugs, antihistamine/antipruritic drugs, immunosuppressants, antimetabolite cytotoxics, neuroprotective agents, T cell inhibitors, antimigraine agents, antiarthritic agents, antigout agents, anticoagulants, thrombolytic agents, antifibrinolytic agents, hemorheologic agents, antiplatelet agents, anticonvulsants, agents useful for calcium regulation, antibacterial agents, antifungal agents, antiviral agents, antimicrobials, anti-infectives, bronchodialators, hormones, hypoglycemic agents, hypolipidemic agents, proteins, nucleic acids, agents useful for erythropoiesis stimulation, antiulcer/antireflux agents, antinauseants/antiemetics, agents useful for treating septic shock, agents useful for treating multiple sclerosis, anti-allograft rejection agents, agents useful for treatment of systemic lupus erythematosus (SLE), agents useful for treating Alzheimer's disease, antiparkinson agents, agents useful for treating psoriasis, agents useful for treating diabetes, anti-stroke agents, agents useful for the treatment of carcinomas, agents useful for the treatment of endometriosis, agents useful for the treatment of uterine contraction, agents useful for the treatment of diuresis, agents useful for the treatment of cystic fibrosis, agents useful for the treatment of neutropenia, agents useful for the treatment of cancer, agents useful for the treatment of respiratory disorders, agents useful

for the treatment of ischemia/reperfusion injury, agents useful for the treatment of ophthalmic diseases, agents useful for the treatment of cardiovascular diseases, anti-inflammatory agents or antioxidants.

3. A compound according to claim 1 wherein said pharmacologically active agent is a non-steroidal antiflammatory drug, an antihypertensive agent, an antineoplastic agent, an anti-allograft rejection agent, a neuroprotective agent, an immunosuppressive agent or an antioxidant.

4. A compound according to claim 1 wherein said pharmacologically active agent is aspirin, ibuprofen, ketoprofen, diclofenac, adriamycin, cyclosporin, FK506, LFA-1, selectin inhibitors or tissue plasminogen activator.

5. A compound comprising a cleavable thiocarbonyl sulfide derivative of a pharmacologically active agent.

6. A compound comprising a thiocarbonyl sulfide substituted pharmacologically active agent, wherein said compound is susceptible to cleavage of carbonyl disulfide therefrom.

7. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier therefor.

8. A composition according to claim 7 wherein said pharmaceutically acceptable carrier is selected from a solid, solution, emulsion, dispersion, micelle or liposome.

9. A composition according to claim 7 wherein said composition further comprises an enteric coating.

10. In the administration of a pharmacologically active agent to a subject for the treatment of a pathological condition, the improvement comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent prior to administration of said pharmacologically active agent to said subject, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions, thereby releasing a therapeutically effective amount of carbon disulfide.

11. A method according to claim 10 wherein said pharmacologically active agent is administered orally.

12. A method according to claim 10 wherein said pharmacologically active agent is administered intravenously, subcutaneously, parenterally, rectally or by inhalation.

13. In the treatment of a subject suffering from a pathological condition by administration thereto of a pharmacologically active agent, the improvement comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent prior to administration thereof to said subject, wherein said covalent attachment is susceptible to cleavage under selected physiological conditions, thereby releasing a therapeutically effective amount of carbon disulfide.

14. A method for the treatment of a subject afflicted with a pathological condition, said method comprising administering to said subject an effective amount of a modified pharmacologically active agent,

wherein said pharmacologically active agent is effective for treatment of said condition,

wherein said pharmacologically active agent has been modified by the covalent attachment thereto of a thiocarbonyl sulfide substituent, and

wherein said covalent attachment is susceptible to cleavage under selected physiological conditions, thereby releasing a therapeutically effective amount of carbon disulfide.

15. A method for the preparation of a protected form of a pharmacologically active agent, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent,

wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

16. A method for reducing the side effects induced by administration of a pharmacologically active agent to a subject, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent prior to administration to said subject,

wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

17. A method for enhancing the effectiveness of a pharmacologically active agent, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent,

wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

18. A method for reducing liver injury caused by administration of pharmacologically active agent(s) to a subject, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent prior to administration to said subject,

wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

19. A method for enhancing circulating levels of pharmacologically active agent(s) upon administration to a subject, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent prior to administration thereof to said subject,

wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

20. A method to prolong the presence in the circulatory system of a subject of a pharmacologically active agent administered to said subject, said method comprising covalently attaching a thiocarbonyl sulfide substituent to said pharmacologically active agent,

wherein said covalent attachment is susceptible to cleavage under selected physiological conditions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/02678

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A01N 37/10; C07C 321/16
US CL :514/570; 562/426, 431
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/570; 562/426, 431

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

file cluster MEDICINE on STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,411,947 A (HOSTETLER ET AL) 02 May 1995 (02/05/95), see entire document	1-20
A,P	US 5,744,592 (HOSTETLER ET AL) 28 April 1998 (28/04/98), see entire document	1-20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
31 MARCH 1999	03 MAY 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BRIAN J. DAVIS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*